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PATENT

Attorney Docket No. NATNUT-03972 10/24/01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Jan Wadstein *et al.*
Serial No.: 09/410,484 Group No.: 1614
Filed: 09/30/99 Examiner: H. Nguyen
Entitled: **Method Of Treating Hypertension And Reducing Serum Lipase Activity**

Declaration of Dr. Yan Dong and Dr. Clement IP

Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.10

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number , addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231

Dated: 10-15-01 By: Mary Ellen Waite

We, Dr. Yan Dong and Dr. Clement Ip, state as follows:

1. Our present positions are in the Dept. of Experimental Pathology, Roswell Park Cancer Institute. Our Cirriculum Vitae are attached hereto at Tabs 1 and 2 respectively.

2. We have reviewed the Office Action mailed July 20, 2001 for the above captioned patent application. It is our understanding that in the Office Action the Examiner stated methods of treating hypertension with CLA are obvious in view of the Langer and Udell references because it is obvious "to use CLA in the method of reducing blood pressure by losing weight of Langer to achieve the beneficial effect of weight loss by taking CLA in view of Udell."

3. We have read both of the cited references and conclude that the Examiner's reasoning regarding the Langer and Udell references is not based on sound scientific reasoning. The references do not provide any teaching or suggestion of treating hypertension with CLA. The Examiner's reasoning is scientifically flawed because a link cannot be drawn between the body composition altering effects of CLA described in Udell and the weak correlation

between weight and hypertension described in Langer. Our own research, conducted after the filing of the above referenced application with materials provided by the applicants, indicates that the effect of CLA on blood pressure most likely occurs through the regulation of key enzymes. This research is described below.

4. Female Sprague-Dawley rats were fed either a control basal diet (no CLA) or the same diet containing 1% 9,11-CLA or 10,12-CLA for 1 month. At necropsy, the mammary gland was removed and frozen immediately in liquid nitrogen. The frozen sample was pulverized and homogenized with a Polytron tissue grinder. Total RNA was isolated with the use of TRIzol® reagent (Life Technologies, Inc.) according to the procedure supplied by the manufacturer.

mRNA was poly(A)+-selected from the total RNA sample with Oligotex mRNA isolation system (Qiagen), and subjected to double-stranded cDNA synthesis using Superscript Choice cDNA synthesis kit (GIBCO/BRL) with an HPLC-purified oligo(dT)24 anchored T7 primer (GENSET). The use of high quality HPLC-purified primer ensured a good double-stranded cDNA synthesis as well as a high in vitro transcription yield. Biotinylated cRNA probes, in vitro transcribed from each cDNA sample using the RNA transcript labeling kit (BioArray) in the presence of biotin-11-CTP and biotin-16-UTP, were purified using RNeasy spin column (Qiagen) to remove unincorporated NTPs. Each purified biotinylated cRNA probe was fragmented by mild alkaline treatment to avoid tertiary structures and to achieve optimal hybridization. The Affymetrix rat genome U34A GeneChip (containing about 7,000 known genes) was used for the gene expression analysis. Four bacterial and phage cRNAs (referred as "sensitivity spikes") hybridizable to probes spotted for control purpose on the chip were added to the probe mixture at known concentrations to monitor hybridization efficiency, per instruction of the manufacturer (Affymetrix). After hybridization with the probe mixture and a high-stringency wash, the chip was stained with streptavidin-phycoerythrein (Molecular Probes). Fluorescence intensities were captured with a laser confocal scanner (Hewlett Packard) and subjected to data analysis.

Each scanned image was analyzed independently with Affymetrix Microarray Suite software. The individual hybridization signal intensity (perfect match intensity minus mismatch intensity) was calculated for each probe pair. The expression value for each gene

was determined by calculating the mean of hybridization signal intensities among its representative 25-mer oligonucleotide probe sets. A tabular report of the magnitude of change for each gene was generated by dividing the expression value in the CLA group by that of its corresponding control group. The mRNA signals of the following genes were all DECREASED by either 9,11-CLA or 10,12-CLA. The numbers represent the fold of change compared to the control (i.e. no CLA).

Experimental Results		
Gene	**c9,t11 CLA**	**t10,c12 CLA**
angiotensinogen	6.2	2.3
angiotensin converting enzyme		2.3
angiotensin I receptor	4.7	2.2
angiotensin II receptor	5.5	
endothelin converting enzyme		2.0
ET-B endothelin receptor		3.7

6. The experiment described above demonstrates that exposure of the mammary gland cells of rats to CLA isomers results in the down regulation of genes which are known to be involved in regulating blood pressure. Thus, the blood pressure lowering activity of CLA may be due to a direct effect at the gene regulation level and may not be due to the overall effect of weight loss as suggested by the Examiner.

7. We further declare that all statement made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of title 18 of the

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United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Clement Ip

Dr. Clement Ip

Date: Oct. 11, 2001

Yan Dong

Dr. Yan Dong

Date: 10/11/01

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Yan Dong	Post-doctoral Research Fellow

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Jilin University, Jilin, PR China	B.S.	1992	Molecular Biology
University of Science & Technology of China, Chinese Academy of Science, Beijing	M.S.	1994	Molecular Biology
SUNY at Buffalo, Roswell Park Graduate Division	Ph.D.	1999	Molecular Biology

Professional Positions:

1999-present, Post-doctoral Research Affiliate, Dept. of Experimental Pathology, Roswell Park Cancer Institute, Buffalo, NY

Research Experience:

1991-1992, Purification of a heat-stable α-amylase and assessing its heat-stability.
1992-1994, Kinetics study of the alteration in fatty acid synthase activity during liver development, and determination of the underlying mechanism.
1994-1999, Identification of molecular basis for widespread loss of a tumor suppressor, gelsolin, in breast cancers.

Awards and Other Professional Activities:

1990-1991 Best Achievement in Student Leadership
1990-1992 University Scholarship for Outstanding Students
1992-1994 President Scholarship for Outstanding Students
1997-1999 Mark Diamond Research Foundation Award
1994-1999 New York State Training Fellowship
1999 Eastern Student Research Forum Honorable Mention Prize and Travel Award
1999 RPCI Student Poster Competition First Place Prize
2001-2002 AACR-Cancer Research Foundation of America Fellowship in Prevention Research

Research Techniques:

***Molecular and Cellular Biology*:** cDNA microarray analysis; Mammalian tissue culture techniques; recombinant DNA technology; nucleic acid isolation; Northern, Southern and Southwestern blot analysis; PCR; DNA sequencing; mammalian cell transfection techniques; reporter gene assay; nuclear run-on assay; mRNA stability assay; electrophoresis mobility shift assay; footprinting; site-directed DNA mutagenesis; RT-PCR; 5'- and 3'- RACE; DNase I hypersensitivity assay; Erase-A-Base cloning technique; MTT assay.

Biochemistry: Western blot analysis; SDS-PAGE; ELISA; immunohistochemistry; enzyme kinetics; protein purification and quantitation; affinity chromatography; ion exchange chromatography; gel filtration chromatography.

Other Techniques: Protein and nucleic acid sequence analysis; PhosphorImaging; Densitometry; computer vision and image analysis.

Publications:

Asch, H.L., Head, K.H., Dong, Y., Winston, J., Connolly, J.L., and Asch, B.B. (1996) Widespread loss of gelsolin in breast cancers of humans, mice and rats. *Cancer Res., 56: 4841-4845.*

Dong, Y., Asch, H.L., Medina, D., Ip, C., Ip, M., Guzman, R., and Asch, B.B. (1999) Concurrent deregulation of gelsolin and cyclin D1 in the majority of human and rodent breast cancers. *International Journal of Cancer, 81: 930-938.*

Dong, Y., Lisk, D., Block, E., Ip, C. (2001) Characterization of the biological activity of γ-glutamyl-*Se*-methylselenocysteine: A novel naturally occurring anticancer agent from garlic. *Cancer Res., 61: 2923-2928.*

Ip, C., Dong, Y. (2001) Methylselenocysteine modulates proliferation and apoptosis biomarkers in premalignant lesions of the rat mammary gland. *Anticancer Res., 21: 863-868.*

Ip, C., Dong, Y., Thompson, H.J., Bauman, D.E., Ip, M.M. (2001) Control of rat mammary epithelium proliferation by conjugated linoleic acid. *Nutr. Cancer, 39: 233-238.*

Dong, Y., Asch, H.L., Asch, B.B. (2001) Molecular basis for loss of gelsolin in breast cancer cells. *Submitted.*

Abstracts:

Dong, Y., Ip, C., Medina, D., Guzman, R., Asch, H.L., and Asch, B.B. (1998) Deregulation of Gelsolin and Cyclin D1 are Molecular Defects Common to the Majority of Breast Cancers in Humans and Rodents. *Proceedings of the American Association for Cancer Research, 39: 619.*

Dong, Y., Asch, H.L., Asch, B.B. (1999) Proximal Promoter Sequences Mediate Reduced Expression of the Tumor Suppressor Gelsolin in Human Breast Cancer Cells. *Proceedings of the American Association for Cancer Research, 40: 367.*

Dong, Y. and Ip, C. (2001) The Use of Microarray Analysis in Delineating the Molecular Effects of Selenium Chemoprevention. *Proceedings of the American Association for Cancer Research, 42: 308.*

Presentations:

RPCI Breast Program Retreat, May, 1997, East Aurora, New York. Poster presentation, "Defects Common to Breast Cancer of Humans and Rodents", Dong Y., Ip C., Medina D., Guzman R., Asch H.L., and Asch B.B.

14th Gordon Research Conference on Mammary Gland Biology, June 1997, Plymouth, New Hampshire. Poster presentation, "Concurrent Deregulation of Gelsolin and Cyclin D1 in Breast Cancers", Dong Y., Ip C., Medina D., Guzman R., Asch H.L., and Asch B.B.

89th Annual Meeting of American Association for Cancer Research, March, 1998, New Orleans, Louisiana. Poster Presentation, "Deregulation of Gelsolin and Cyclin D1 are Molecular Defects Common to the Majority of Breast Cancers in Humans and Rodents", Dong Y., Ip C., Medina D., Guzman R., Asch H.L., and Asch B.B.

25th Eastern Student Research Forum, February, 1999, Miami, Florida. Oral Presentation, "Molecular Basis For Widespread Loss of Gelsolin in Human Breast Cancers", Dong Y., Asch H.L., Asch B.B.

90th Annual Meeting of American Association for Cancer Research, April, 1999, Philadelphia, Pennsylvania. Poster Presentation, "Proximal Promoter Sequences Mediate Reduced Expression of the Tumor Suppressor Gelsolin in Human Breast Cancer Cells", Dong Y., Asch H.L., Asch B.B.

15th Gordon Research Conference on Mammary Gland Biology, June 1999, Henneker, New Hampshire. Poster presentation, "Molecular Basis For Widespread Loss of Gelsolin In Human Breast Cancers", Dong Y., Asch H.L., and Asch B.B.

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NAME	POSITION TITLE
Yan Dong	Post-doctoral Research Fellow

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Jilin University, Jilin, PR China	B.S.	1992	Molecular Biology
University of Science & Technology of China, Chinese Academy of Science, Beijing	M.S.	1994	Molecular Biology
SUNY at Buffalo, Roswell Park Graduate Division	Ph.D.	1999	Molecular Biology

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Dong, Y., Lisk, D., Block, E., Ip, C. (2001) Characterization of the biological activity of γ-glutamyl-*Se*-methylselenocysteine: A novel naturally occurring anticancer agent from garlic. *Cancer Res., 61: 2923-2928.*

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15th Gordon Research Conference on Mammary Gland Biology, June 1999, Henneker, New Hampshire. Poster presentation, "Molecular Basis For Widespread Loss of Gelsolin In Human Breast Cancers", Dong Y., Asch H.L., and Asch B.B.

Principal Investigator/Program Director (Last, first, middle): Ip, Clement

BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Clement Ip	Associate Member of Clinical Research

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
McGill University, Montreal	B.Sc.	1969	Biochemistry
University of Wisconsin, Madison	Ph.D.	1973	Nutritional Biochemistry
Upstate Medical Center, Syracuse	Postdoc.	1973-1975	Nutritional Biochemistry

Professional positions
Dept. of Breast Surgery, 1975-1997; Dept. of Experimental Pathology, 1998-
Roswell Park Cancer Institute, Buffalo, NY

Professional membership
American Association for Cancer Research
American Society for Nutritional Sciences

Recent selected services in outside committees
NIH DRG Metabolic Pathology Study Section, 1990-1994
NIH DRG Reviewer Reserve, 1994-1998
US Army Medical Research and Materiel Command - Breast Cancer Research Program Review, 1994-1999
US Army Medical Research and Materiel Command – Prostate Cancer Research Program Review, 1997-1999
University of California - Breast Cancer Research Program Review, 1995-1997
Ad hoc membership on numerous NCI grant review committees and program project site visits
Associate Editor, *Nutrition and Cancer*, 1994-present
Editorial Board, *The Journal of Nutrition*, 1997-1999
American Cancer Society – Carcinogenesis, Nutrition and Environment Study Section, 1999-2002

Publications
There are a total of 137 full-length publications since 1973. The following is a list of papers from 1999 to 2001.

Banni, S., Angioni, E., Casu, V., Melis, M.P., Scrugli, S., Carta, G., Corongiu, F.P. and Ip, C. (1999) An increase in vitamin A status by the feeding of conjugated linoleic acid. Nutr. Cancer 33: 53-57.

Ip, M.M., Masso-Welch, P.A., Shoemaker, S.F., Shea-Eaton, W.K. and Ip, C. (1999) Conjugated linoleic acid inhibits proliferation and induces apoptosis of normal rat mammary epithelial cells in primary culture. Exp. Cell Res. 250: 22-34.

Banni, S., Angioni, E., Casu, V., Melis, M.P., Carta, G., Corongiu, F.P., Thompson, H. and Ip, C. (1999) Decrease in linoleic acid metabolites as a potential mechanism in cancer risk reduction by conjugated linoleic acid. Carcinogenesis 20: 1019-1024.

Dong, Y., Asch, H.L., Medina, D., Ip, C., Ip, M., Guzman, R. and Asch, B.B. (1999) Concurrent deregulation of gelsolin and cyclin D1 in the majority of human and rodent breast cancers. Int. J. Cancer 81: 930-938.

Ip, C., Zhu, Z., Thompson, H.J., Lisk, D. and Ganther, H.E. (1999) Chemoprevention of mammary cancer with Se-allylselenocysteine and other selenoamino acids in the rat. Anticancer Res. 19: 2875-2880.

Ip, C., Banni, S., Angioni, E., Carta, G., McGinley, J., Thompson, H.J., Barbano, D. and Bauman, D. (1999) Conjugated linoleic acid-enriched butter fat alters mammary gland morphogenesis and reduces cancer risk in rats. J. Nutr. 129: 2135-2142.

Jiang, C., Jiang, W., Ip, C., Ganther, H. and Lu, J. (1999) Selenium-induced inhibition of angiogenesis in mammary cancer at chemopreventive levels of intake. Mol. Carcinogen. 26: 213-225.

Ip, C., Thompson, H.J. and Ganther, H.E. (2000) Selenium modulation of cell proliferation and cell cycle biomarkers in normal and premalignant cells of the rat mammary gland. Cancer Epidemiol. Biomarkers Prev. 9: 49-54.

Ip, C., Birringer, M., Block, E., Kotrebai, M., Tyson, J.F., Uden, P.C. and Lisk, D.J. (2000) Chemical speciation influences comparative activity of selenium-enriched garlic and yeast in mammary cancer prevention. J. Agr. Food Chem. 48: 2062-2070.

Ip, C., Thompson, H.J., Zhu, Z. and Ganther, H.E. (2000) In vitro and in vivo studies of methylseleninic acid: Evidence that a monomethylated selenium metabolite is critical for cancer chemoprevention. Cancer Res. 60: 2882-2886.

Ip, C., Ip, M.M., Loftus, T., Shoemaker, S. and Shea-Eaton, W. (2000) Induction of apoptosis by conjugated linoleic acid in cultured mammary tumor cells and premalignant lesions of the rat mammary gland. Cancer Epidemiol. Biomarkers Prev. 9: 689-696, 2000.

Mansoor, S., Ip, C. and Stomper, P.C. (2000) Yield of terminal ductal lobule units in normal breast stereotactic core biopsy specimens: Implications for biomarker studies. Breast J. 6: 220-224.

Zhu, Z., Jiang, W., Ganther, H.E., Ip, C. and Thompson, H.J. (2000) *In vitro* effects of Se-allylselenocysteine and Se-propylselenocysteine on cell growth, DNA integrity, and apoptosis. Biochem. Pharmacol. 60: 1467-1473.

Livisay, S.A., Zhou, S.Y., Ip, C. and Decker, E.A. (2000) Impact of dietary conjugated linoleic acid on the oxidative stability of rat liver microsomes and skeletal muscle homogenates. J. Agr. Food Chem. 48: 4162-4167.

Whanger, P.D., Ip, C., Polan, C.E., Uden, P.C. and Welbaum, G. (2000) Tumorigenesis, metabolism, speciation, bioavailability, and tissue deposition of selenium in selenium-enriched ramps (*Allium tricoccum*). J. Agr. Food Chem. 48: 5723-5730.

Zhu, Z., Jiang, W., Ganther, H.E., Ip, C. and Thompson, H.J. (2000) Activity of Se-allylselenocysteine in the presence of methionine γ-lyase on cell growth, DNA integrity, apoptosis, and cell-cycle regulatory molecules. Mol. Carcinogen. 29: 191-197.

Ip, C., Lisk, D.J. and Ganther, H.E. (2000) Chemoprevention with triphenylselenonium chloride in selenium-deficient rats. Anticancer Res. 20: 4179-4182.

Jiang, W., Zhu, Z., Ganther, H.E., Ip, C. and Thompson, H.J. (2001) Molecular mechanisms associated with Se-allylselenocysteine regulation of cell proliferation and apoptosis. Cancer Lett. 162: 167-173.

Ganther, H.E. and Ip, C. (2001) Thioredoxin reductase activity in rat liver is not affected by supranutritional levels of monomethylated selenium in vivo and is inhibited only by high levels of selenium in vitro. J. Nutr. 131: 301-304.

Dong, Y., Lisk, D.J., Block, E. and Ip, C. (2001) Characterization of the biological activity of γ-glutamyl-*Se*-methylselenocysteine: A novel naturally occurring anticancer agent from garlic. Cancer Res. 61: 2923-2928.

Ip, C. and Dong, Y. (2001) Methylselenocysteine modulates proliferation and apoptosis biomarkers in premalignant lesions of the rat mammary gland. Anticancer Res. 21: 863-867.

Finley, J.W., Ip, C., Lisk, D.J., Davis, C.D., Hintze, K.J., and Whanger, P.D. (2001) Cancer-protective properties of high-selenium broccoli. J. Agr. Food Chem. 49: 2679-2683.

Banni, S., Carta, G., Angioni, E., Murru, E., Scanu, P., Melis, M.P., Bauman, D.E., Fischer, S.M. and Ip, C. (2001) Distribution of conjugated linoleic acid and metabolites in different lipid fractions in the rat liver. J. Lipid Res. 42: 1056-1061.

Ip, C., Dong, Y., Thompson, H.J., Bauman, D.E., Ip, M.M. (2001) Control of rat mammary epithelium proliferation by conjugated linoleic acid. Nutr. Cancer 39: 233-238.